Scientific Basis of Clinical Practice

Iatrogenic Misadventure

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A striking feature of the history of therapeutics is the extent to which fashion, rather than clinical science, governs the treatment we mete out to our patients. Some ten years ago I attended a symposium on anticoagulant therapy and returned home firmly convinced that in all but a very few conditions such treatment was absolutely essential and indeed it was little short of criminal negligence to withhold it. At that time the patient queue for "prothrombin times" was usually the longest in our hospitals and phenindione was among the most frequently prescribed drugs, but our constant use of it stemmed from enthusiasm and ignorance of its dangers and not from scientific proof of its therapeutic advantages. Indeed it is only as knowledge has accumulated that we have learned of the toxic effects, of the drug we gave so freely, on the kidney, the liver, the bone marrow, and the skin and that except in thromboembolic disease and in patients with prosthetic heart valves the dangers of any form of anticoagulant therapy far outweigh any therapeutic benefits it may confer.

Fortunately no count has been kept of the pints and pints of blood which had to be given to replace that lost from peptic ulcers and hiatal hernias provoked to bleed by our misdirected measures or of the joints we have stiffened by haemarthrosis or of those whose meeting with their maker we have brought forward by iatrogenic cerebral haemorrhage. Indeed, it is only now when anticoagulant therapy has been abandoned except in a very limited field that we have learned of the complexities surrounding its use—particularly the interaction of anticoagulants with other drugs. Much of orally administered anticoagulant drugs—such as the current favourite, warfarin—become bound to the plasma proteins and it is only that part not so bound that is pharmacologically active. Nevertheless, if another acidic drug with a greater affinity for the plasma proteins such as clofibrate, phenylbutazone, indomethacin, salicylates, mefenamic acid, sulphonamides, ethacrynic acid, or diazoxide is given concurrently this will displace the protein-bound fraction of warfarin and may so enhance its anticoagulant effect as to produce dangerous haemmorhage.

On the other hand, a wide variety of sedatives, tranquillizers and antidepressants such as the barbiturates, glutethimide, diphenhydramine, and meprobamate by enzyme induction inactivate oral anti-coagulants and their withdrawal or intermittent use may provoke serious haemmorhage. Chloral competes with warfarin for its binding sites on the plasma proteins and so tends to increase anticoagulation but the effect of dichloralphenazone, which is a combination of antipyrine and chloral, is unpredictable as antipyrine has enzyme-inducing effects. No one would pretend that our knowledge of drugs interacting with oral anticoagulants is complete. Even so, sufficient is already known to indicate that anticoagulant drugs have potent dangers and should be used only within the limited sphere in which they are of proven worth. Moreover, when they are given, if possible, no other drug should be given at the same time as many are known to inhibit or enhance their effect and many others may have similar interactions, even though these are as yet unrecognized and unreported.

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Hypotensive Drugs

Hypotensive drugs are being used increasingly and undoubtedly their development has provided an enormous advance both in the treatment and in the prognosis of the severe forms of hypertension—particularly in the younger age groups. Unfortunately, hypotensive drugs, like all other effective forms of medication, can do harm as well as good and the finding of raised systolic or diastolic pressure, or both, is certainly not an absolute indication for hypotensive therapy. The lowering of arterial blood pressure often provokes cerebral infarction in those with carotid or vertebrobasilar disease and myocardial infarction in those whose coronary arteries are narrowed by atheroma. Most older patients have some arterial degenerative change which makes lowering of the blood pressure immeasurably more hazardous than leaving the level alone and the administration of hypotensive drugs over the age of 60 is not often advantageous. The systolic hypertension of the aged is a simple physiological adjustment to increased peripheral arterial resistance, and Professor Ferguson Anderson's statement that the only benefit that accrues from hypotensive drugs in older people is when their administration is stopped is usually true.

Apart from the dangers of provoking cerebral or myocardial infarction hypotensive drugs may have many other damaging effects. Rawolfia derivatives and methyldopa may cause depression sometimes of suicidal degree, while guanethidine and bethanidine may cause hypotensive syncope on standing up or during exercise to such an extent that the patients' self confidence and capacity to lead a normal life are completely undermined. Most hypotensive drugs are destructive of sexual function in the man and this may be a potent source of unhappiness. The anxious patient may focus his worries on his hypotensive therapy and feel infinitely less well than he was without treatment. The toxic effects of hypotensive drugs such as fluid retention, fever, rashes, diarrhoea, etc., are all well known. In the next decade better hypotensive drugs may well become available and their justifiable employment may be widened; but today we should remember the good prognosis of untreated benign hypertension, particularly in women, the dangers and side effects of hypotensive drugs, particularly in the aged, and we should tend to restrict their use to younger people with the more severe grades of hypertension.

Steroids

When corticosteroids became available they were the touch of Jesus to patients suffering from Addison's disease and panhypopituitarism, but, as with every therapeutic weapon given to doctors, they quickly became the "latest" treatment for every disease for which we had no cure. It would occupy a whole edition of the *B.M.J.* to enumerate all the conditions in which they have been employed but a few lines would suffice to encompass the diseases in which their efficacy is proved. A whole series of editions would, however, be occupied by a description of the havoc they have wrought, despite the best intentions and the most ethical therapeutic endeavours of those who have prescribed them.

The inevitable and progressive loss of calcium from the skeleton which follows steroid therapy and the certain knowledge that such calcium can never be replaced, the high incidence of peptic ulceration, of ruptured colonic diverticula, of oedema, diabetes, hypertension, posterior polar cataract, proximal myopathy, psychiatric disorders, skin damage, purpura, venous thrombosis, tendo achillis rupture, etc. should cause us all to hesitate, indeed should usually dissuade us—from prescribing corticosteroids or corticotrophin. Moreover, when we do prescribe them our knowledge of their iatrogenic dangers should make us constantly want to reduce the dose or withdraw the drug altogether. It would be quite inappropriate to discuss here the circumstances in which steroid therapy should or should not be employed. Many times we have all seen the lives of patients in status asthmaticus saved with corticotrophin, patients with ulcerative colitis brought into remission with steroid retention enemata, patients desperately ill with the acute manifestations of systemic lupus erythematosus rapidly restored to normal health by corticosteroids. Our duty is to be fully aware of the terrible dangers of steroid therapy, particularly on a long-term basis, to appreciate the limited number of disorders it may benefit, and to withdraw it or attempt to withdraw it as soon as its inefficacy has been established or the condition for which it was given has been brought under control.

Myxoedema

The importance of myxoedema is the frequency with which it escapes diagnosis and the ease with which it can be cured. Many with subnormal thyroid function never seek medical attention, and when they do general practitioners, physicians, and psychiatrists of the utmost competence often fail to recognize the condition and after a long period of poor health one of the spells of arctic climate which come to England once or twice in each decade may bring the patient's life to an end in hypothermic coma. Though myxoedema may arise from Hashimoto's thyroiditis or idiopathically, in most patients it is iatrogenic in origin resulting either from partial thyroidectomy or from treatment with radioactive iodine. We must accept the fact that relatively many patients so treated for thyrotoxicocis develop myxoedema and that this may be an unrecognized and serious source of ill health. All these patients should be seen either by their general practitioner, surgeon, radiotherapist, or physician once every year for the rest of their lives and their serum protein-bound iodine should be measured on each occasion. Only thus can we give the efficient service to our hyperthyroid patients that we should all like to give. Fortunately most of the "red herrings" raised by abnormal serum protein-bound iodines arise from high levels resulting from medication or radiological investigations and a low figure nearly always means subnormal thyroid function.

Hypoparathyroidism usually follows inadvertent removal of the parathyroid glands during surgical treatment of hyperthyroidism or cancer of the thyroid. Tetany during the immediate postoperative period is the usual manifestation, but the late Professor Paul Forman suggested that much apparently neurotic ill health after thyroid surgery was due to iatrogenic hypoparathyroidism. Thus in patients who continue to complain of symptoms after an operation for goitre it is always worthwhile estimating the serum calcium and phosphorus in the hope that the symptoms are of one's own making and to some extent remediable.

Hepatotoxic Drugs

Two decades ago whenever confronted with a jaundiced patient the physician's diagnostic reaction was "infective hepatitis, gallstones, malignancy, or haemolysis." Today his first thoughts, particularly in the absence of pain, are what drugs has the patient been taking, what anaesthetics may he have had, or what injections may he have been given? Improved sterilization techniques and improved selection of blood donors have reduced serum hepatitis to a fraction of its former incidence, but chlorpromazine, and other antidepressants and tranquillizers, halothane, androgens, and other drugs in common use produce a clinical picture difficult to differentiate from primary organic disease of the extrahepatic biliary system or the liver. Occasionally drug-induced cholestatic jaundice may be extremely protracted and pose a most difficult diagnostic and therapeutic problem.

Drugs We Used to Think "Safe"

The history of therapeutics abounds with records of drugs thought at first to be wholly innocuous and later shown to have devastatingly harmful potentialities. Aspirin for decades the panacea for insomnia, for headaches whatever their origin, for fever whatever its cause, and for "rheumatism" whatever its nature, has been proved beyond doubt to be a powerful gastric irritant capable of causing serious gastroduodenal haemorrhage whether pre-existing peptic ulceration is present or not. Phenacetin, long second to aspirin in the "analgesic league" and a powerful "prop" to the neurotic and the arthritic, after enjoying a blameless reputation for a quarter of a century, has been established as the usual causal factor in papillitis necroticans and analgesic nephropathy—renal pathology largely irreversible even when the nephrotoxic agent in discontinued. Forty or 50 years ago vitamin D was very extensively prescribed and overdosage was unrecognized. Today we all appreciate that it should be used only in the now rare diseases rickets and osteomalacia—and that even then dosage should be carefully controlled by estimations of the blood calcium at sufficiently frequent intervals to preclude the production of sustained hypercalcaemia and nephrocalcinosis.

The physician of the 1970's has potent therapeutic weapons at his disposal, but every effective form of treatment has built-into its chemical structure an inescapable but lesser capacity to cause injurious effects. The insatiable appetite of the populace for a drug for every symptom that they experience should not lead us to prescribe without carefully considering and balancing the need for treatment and the efficacy and dangers of what we prescribe. Every year leaves increasing doubt whether anything is a harmless placebo.

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